a polynucleotide amplification reaction chamber, in fluid communication with said flow channel;

said chamber and said channel being of dissimilar dimension; and

a fluid exit port in fluid communication with said flow system; and

means for thermally cycling the contents of said chamber whereby, in each cycle, temperature is controlled to dehybridize double stranded polynucleotide, and to permit synthesis of polynucleotide, thereby to amplify said preselected polynucleotide.--

REMARKS

The foregoing amendment amends claim 94 and 103 in order to obviate their rejection under the second paragraph of 35 U.S.C. § 112 and adds a new claim 106 which corresponds exactly to the proposed Count of an interference which Applicants are seeking to provoke with U.S. Patent No. 5,498,392.

As noted below, claims 94 and 103 were essentially "copied" from claim 2 of Wilding et al. U.S. Patent No. 5,498,392. The term "sample nucleotide" does not actually appear in either claim 1 or claim 2 of the '392 patent; said term is a shortening of "preselected polynucleotide in a sample". At any rate, what is intended by the term is a single strand of a dehybridized preselected polynucleotide and the foregoing amendment makes this clear.

Claims 93-105 have been rejected under the second paragraph of 35 U.S.C. § 112 as containing subject matter not described in the specification. Specifically, the Examiner is alleging that the term "preselected polynucleotide" is new matter. This rejection is respectfully traversed as follows.

It is conceded that the actual term "preselected polynucleotide" will not be found in Applicants' specification. However, the test for determining whether a term is new matter is not based on the actual words; rather, it is based on the meaning of the proposed term. A term in an added claim is not new matter if the term is inherently present in the specification as filed. This is indeed the case with "preselected polynucleotide". The Examiner's attention is directed to the following passage from Applicants' application:

> PCR can selectively amplify a single molecule DNA (or RNA) of an organism by a factor of 10^6 to 10^9. This well-established procedure requires the repetition of heating (denaturing) and cooling (annealing) cycles in the presence of an original DNA target molecule, specific DNA primers, deoxynucleotide triphosphates, and DNA polymerase enzymes and cofactors. Each cycle produces a doubling of the target DNA sequence, leading to an exponential accumulation of the target sequence.

Page 3, line 33, to page 4, line 9. This passage is a summation of what the polymerase chain reaction does. Clearly, the term "target DNA sequence" is, in this context, synonymous with the term "preselected polynucleotide" as used in Wilding et al. U.S. Patent No. 5,498,392.

Claims 81, 82, 85-87 and 93-105 have been rejected under 35 U.S.C. § 102(d) as anticipated by the '392 patent. Applicants are seeking to provoke an interference with said patent. Applicants accordingly request that action based on said alleged anticipation be suspended pending the outcome of the interference.

Claims 83 and 84 have been indicated as allowable pending their rewriting. The claims have been so amended.

COMPLIANCE WITH 37 CFR § 1.607

Under the provisions of 37 CFR § 1.607(a), Applicants seek to have an interference declared between their present application and U.S. Patent No. 5,498,392, granted March 12, 1996, to Peter Wilding and Larry Kricka ("Wilding") (Appendix A).

The information required by 37 CFR § 1.607(a) is set forth under headings which correspond to the relevant subsections of 37 CFR § 1.607(a).

(1) Identification of the Interfering Patent: The patent which claims subject matter interfering with the subject matter claimed in the instant application is U.S. Patent No. 5,498,392 issued to Peter Wilding and Larry J. Kricka and entitled "Mesoscale Polynucleotide Amplification Device and Method". The Wilding patent was issued on application No. 08/308,199 filed on September 19, 1994 which purports on its face to be a continuation of application No. 07/877,662, now abandoned. The Trustees of the University of Pennsylvania is the assignee named on the face of the patent.

A copy of U.S. Patent No. 5,498,392 is here attached as Appendix A.

Applicants acknowledge that Wilding et al. would, in an interference involving U.S. Patent No. 5,498,392 (hereinafter "the '392 Patent") be entitled to the benefit of the filing date of application No. 07/877,662.

(2) Proposed Count

Pursuant to 37 CFR § 1.607(a)(2), Applicants present the following proposed Count:

A device for amplifying a preselected polynucleotide in a sample, the device comprising:

a solid substrate microfabricated to define:

a sample inlet port;

a flow system for micro- to pico-liter volumes comprising:

a sample flow channel extending from said inlet port; and

a polynucleotide amplification reaction chamber, in fluid communication with said flow channel;

said chamber and said channel being of dissimilar dimension; and

a fluid exit port in fluid communication with said flow system; and

means for thermally cycling the contents of said chamber whereby, in each cycle, temperature is controlled to dehybridize double stranded polynucleotide, and to permit synthesis of polynucleotide, thereby to amplify said preselected polynucleotide.--

A copy of the proposed Count is attached as Appendix B.

The proposed Count is a phantom Count prepared in accordance with MPEP § 2309 in order to encompass the broadest patentable interfering subject matter common to both parties.

(3) The Claims in U.S. Patent No. 5,498,392 which Correspond to the Proposed Count:

Pursuant to 37 C.F.R. § 1.607(a)(3), Applicants submit that all of the claims in the '392 patent correspond substantially to the proposed Count.

The proposed Count has been, to the extent possible, copied from claim 14 of the '392 patent, but with the following changes:

(1) The term "a mesoscale flow system" (column 18, line 5) has been changed to "a flow system for micro- to pico-liter volumes";

(2) The phrase "containing a preselected polynucleotide and polynucleotide amplification reagents" (column 18, lines 9-11) has been omitted; and

(3) The phrase "said sample flow channel and said reaction chamber having at least one cross-sectional dimension of width or depth which is from 0.1 to 500 μm" (column 18, lines 12-14) has been omitted.

The modifications were made in order to ensure that said Count will cover the broadest patentable interfering subject matter of both parties.

Changes (1) and (3) noted above relate to the dimensions of the flow channel and of the reaction chamber. In the '392 patent, they are expressed mainly in terms of linear dimensions. See, for example: column 3, lines 18-29; column 7, lines 46-53; and claims 1, 14, 21 and 25. However, these dimensions are also referred to in terms of their volume. See, for example: column 4, lines 3-8, where the volumes are described as being "in the nanoliter or even picoliter range"; and column 10, lines 41-52 where, in addition to linear dimensions, there are also some volumetric dimensions. Applicants' dimensional references are solely in terms of volume as in, for example: page 4, lines 31-32; page 8, lines 16-20; and page 14, lines 33-35. It is submitted that the term "flow system for micro- to pico-liter volumes" is broad enough to encompass the "mesoscale flow system" of the '392 patent as modified by the specific dimensions set forth in all of its claims.

Change (2) is the omission of the requirement in claim 14 of the '392 patent that the reaction chamber contain a preselected polynucleotide and polynucleotide amplification reagents. This limitation is not present in claims 1 and 3-13 of the '392 patent. Applicants express no opinion at this time as to whether claim 14, with this phrase omitted, would be valid as

issued. However, it is submitted that the proposed Count is patentable over the prior art.

Claim 1 also covers a device for amplifying a preselected polynucleotide in a sample which differs from the device of claim 14 in that (1) it does not have the requirement that the reaction chamber contain a preselected polynucleotide and polynucleotide amplification reagents, and (2) the means for thermally cycling the contents of the chamber is incorporated into the solid substrate, rather than being a separate part of the claimed device. This second difference is implicitly recognized at various points in the specification and was specifically pointed out by the patentees on page 13 of an amendment filed on 24 January 1994:

> Thus, the recitation of a thermal cycling or regulating means in independent claims 1, 25 [patent claim 14] and 33 [patent claim 21], is definite and fully enabled by the specification. The office action states on page 9 that it is unclear whether the device requires the appliance. As disclosed in the specification, the device may comprise a thermal cycling means either in the solid substrate or in the appliance. The scope of the means for thermally cycling recited in the claims includes means such as heating elements, microprocessors and pumps either within the substrate or in the appliance, as disclosed in the specification, as well as equivalents thereof.

(Emphasis added.) The "appliance" is a portion of the claimed device which comprises means for holding the substrate.

Claims 15-20 are all ultimately dependent from claim 14, and claims 2-13 are all ultimately dependent from claim 1.

Claim 21 is a method claim covering the use of a device corresponding to the proposed Count. It is a three-step process, the first step (i) being providing a device similar to that claimed in claim 14 but without the preselected polynucleotide and polynucleotide amplification reagents in the reaction chamber. The preselected polynucleotide and the polynucleotide amplification reagents are delivered to the reaction chamber as step (ii) of the claimed method.

Claims 22-24 are all ultimately dependent from claim 21.

Claim 25 corresponds to the Count and is not patentably distinct from claims 1, 14 and 21. However, this claim does not require a "means for recycling the contents" of the chamber. There is the added requirement that the amplification chamber contain "reagents for amplifying a preselected polynucleotide in vitro". This added phrase corresponds to the term "polynucleotide amplification reaction chamber . . . containing . . . polynucleotide amplification reagents" in claim 14.

Claims 26 and 27 are dependent from claim 25.

(4) Identification of Claims in Application No. 08/482,933 which Correspond to the Proposed Count:

Pursuant to 37 CFR § 1.607(a)(4), Applicants submit that claims 93-105, presented by the Second Supplemental Preliminary Amendment on March 11, 1997, and claim 106 presented herewith correspond to the proposed Count.

Claim 106 corresponds exactly to the proposed Count.

Claims 93-101 are analogous to the following claims of the '392 patent, and correspond to the Count.

Appl. No. 08/482,933	U.S. Patent No. 5,498,392
93	1
94	2
95	9
96	14
97	15
98	21
99	22
100	25
101	26

Claim 93 covers a device which is not patentably distinct from the proposed Count. The only substantive difference is that the "means for thermally cycling the contents of the chamber" is required to be part of the microfabricated solid substrate while the Count and claims 96 and 106 would permit said "means" to be external to solid substrate. As noted above, the file of the '392 patent indicates that the cycling means can be "either in the solid substrate or in the appliance".

Claim 94 and 95 are dependent on claim 93.

Claim 96 covers a device which is not patentably distinct from the Count. It is narrower in scope in that the amplification chamber contains a preselected polynucleotide sample.

Claim 97 is dependent on claim 96.

Claim 98 is a method claim covering use of the device of claim 96.

Claim 99 is dependent on claim 98.

Claim 100 covers a device which is not patentably distinct from the Count. It does not specifically recite the "means for thermally cycling the contents" of the amplification chamber, but there is the added requirement that the amplification chamber contain "reagents for amplifying a preselected polynucleotide in vitro". In this application, claim 100 bears the same relationship to claim 93 and 96 as claim 25 of the '392 patent bears to claims 1 and 14 of said patent.

Claim 102-105 are similar to claims 93-96, respectively, the difference being that the term "for micro- to picoliter volumes" is omitted, thus eliminating the numerically expressed dimensional limitation. It is submitted that the recited numerical limitation is not needed to broadly define the invention since persons skilled in the art understand that polymerase chain reactions must necessarily take place in environments dimensionally suited to the target DNA sequences. These claims also correspond to the proposed Count.

(5) Application of the Terms of Applicants' Newly Present Claim to Applicants' Disclosure:

Applicants previously submitted claims which correspond to the proposed Count have already been reviewed by the Examiner. Attached hereto, as Appendix C, is a table applying the terms of claim 106 to the terms of Applicants' disclosure.

(6) Compliance with 35 USC § 135(b):

Newly-presented claim 106 is for substantially the same subject matter as claim 14 of the '392 patent. Claim 106 corresponds exactly to the proposed Count and the difference between the proposed Count and claim 14 are discussed above under the sub-heading "(3) The Claim in U.S. Patent No. 5,498,392 which Correspond to the Proposed Count". Differences (1) and (3) relate to language only. Difference (2) is an omitted phrase which is also not included in claim 1 of the '392 patent. Accordingly, claim 106 complies with 35 USC § 135(b) and should be entered.

However, if the Examiner does not agree that claim 106 should be entered, the proposed interference can proceed without it.

Conclusion

In the proposed interference, Applicants will be entitled to the benefit of application No. 07/938,106 filed on August 31, 1992, now U.S. Patent No. 5,639,423.

Since the effective filing date of the subject application was filed more than three months after the effective filing date of the application that matured into U.S. Patent No. 5,498,392, Applicants will present evidence complying with 37 CFR § 1.608(b).

Respectfully submitted,

Date: 9/30/98

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APPENDIX B

COUNT

A device for amplifying a preselected polynucleotide in a sample, the device comprising:

a solid substrate microfabricated to define:

a sample inlet port;

a flow system for micro- to pico-liter volumes comprising:

a sample flow channel extending from said inlet port; and

a polynucleotide amplification reaction chamber, in fluid communication with said flow channel;

said chamber and said channel being of dissimilar dimension; and

a fluid exit port in fluid communication with said flow system; and

means for thermally cycling the contents of said chamber whereby, in each cycle, temperature is controlled to dehybridize double stranded polynucleotide, and to permit synthesis of polynucleotide, thereby to amplify said preselected polynucleotide.--

APPENDIX C
37 C.F.R. § 1.607(a)(5)

Claim 106	Appl. No. 08/482,933 (Page No.: Line Nos.)
A device for amplifying a preselected polynucleotide in a sample, the device comprising	(10:21-25) One embodiment of the present invention performs the polymerase chain reaction (PCR). The minute reagent volumes and the specific reaction sequence of the PCR technique play favorably into the advantages of the present invention. (3:33-4:1) PCR can selectively amplify a single molecule of DNA (or RNA) of an organism by a factor of 10^6 to 10^9.
• a solid substrate which is microfabricated to define:	(17:30-33) FIGS. 4(a)-(f) show cross-sectional views of the bottom half of the chamber during successive stages of formation of the chamber 30 from a silicon substrate 50b.
•• a sample inlet port;	Figs. 1 and 2. (14:26-29) The target DNA molecule is placed in reagent chamber 10 by insertion of a hypodermic needle or the like through silicone rubber window 120. (8:33-9:3) A reagent reservoir of the microinstrument may have a thin silicone rubber wall so that the reagent may be inserted into the microinstrument by a hypodermic needle.

Claim 106	Appl. No. 08/482,933 (Page No.: Line Nos.)
•• a flow system for micro- to pico-liter volumes comprising	(8:31-33) The device may be fabricated to allow a continual flow of reagents through the instrument. Fig. 2. (14:33-35) Typically the chambers 10, 12, 14 and 30 have a volume ranging from microliters to nanoliters. (Claim 45) The instrument of claim 26 wherein one of said chambers has a capacity of less than a picoliter.
••• a sample flow channel extending from said inlet port; and	Fig. 2:22. (14:31-33) The reactants in the reagent chambers 10, 12 and 14 are connected by channels 22, 24 and 26 to a reaction chamber 30.
••• a polynucleotide amplification reaction chamber, in fluid communication with said flow channel;	Fig. 2:30. (14:31-33) The reactants in the reagent chambers 10, 12 and 14 are connected by channels 22, 24 and 26 to a reaction chamber 30.
••• said chamber and said flow channel being of dissimilar dimension; and	Shown Fig. 2:22 and 30. *"Dissimilar dimension" is also inherent in the meanings of "chamber" and "channel" when used together in this context.*
•• a fluid exit port in fluid communication with said flow system; and	Fig. 2:32. (15:25-26) A channel 32 connects the reaction chamber 30 to a detection chamber 34.

Claim 106	Appl. No. 08/482,933 (Page No.: Line Nos.)
• means for thermally cycling the contents of said chamber whereby, in each cycle, temperature is controlled to dehybridize double-stranded polynucleotide and to permit synthesis of polynucleotide,	Fig. 2: *heater H_c and Lamb-wave transducer LW_c in reaction chamber 30.* (17:3-11) The PCR reaction is initiated by pumping the reagents in the reagent chambers 10, 12 and 14 along the directions of the arrows to the reaction chamber 30 by activating the reagent pumps LW_1, LW_2 and LW_3. A series of approximately twenty to forty thermal cycles are then initiated, during each cycle the temperature of the reactants in the reaction chamber 30 goes from 55°C to 96°C, and back to 55°C, for example. (4:1-9) This well-established procedure requires the repetition of heating (denaturing) and cooling (annealing) cycles in the presence of an original DNA target molecule, specific DNA primers, deoxynucleotide triphosphates, and DNA polymerase enzymes and cofactors. Each cycle products a doubling of the target DNA sequence, leading to an exponential accumulation of the target sequence.
thereby to amplify said preselected polynucleotide	(3:33-4:1) PCR can selectively amplify a single molecule of DNA (or RNA) of an organism by a factor of 10^6 to 10^9.